**Remarks/Arguments:**

**Interview Summary**

On June 5, 2008, Examiners Ha and Audet agreed to conduct an interview with Applicant's attorneys, Theresa Devlin and Mike Nelson, and James Growcott, Translational Science Strategist in the employment of the Assignee AstraZeneca. Applicant thanks Examiners Ha and Audet for their time and their helpful suggestions. The rejection of Claims 2, 9, 11 and 27 under 35 U.S.C. § 103(a) over Janus *et al,* U.S. Patent Application No. 2002/0055457 in view of Curwen *et al.*, Poster EORTC-NCI-AACR, 2002; Nelson *et al.*, *BJU International* (2000), *85*(suppl. 2), p. 45-48; and Walczak *et al.*, *Expert Opinion* (2002), *11*(12), p. 1737-1748 was discussed.

At the interview, Applicant argued that the claimed combination of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054) and a bisphosphonate resulted in the surprising and unexpected synergy in regard to inhibition of bone metastases in the treatment of prostate cancer. Applicant's arguments in support of the claimed invention were as follow. The bone matrix is a dynamic system which is maintained by a balance of osteoblast activity (cells which build up the bone matrix) and osteoclast activity (cells which break down the bone matrix). Prostate cancer cells that invade the bone matrix release endothelin-1 (ET-1) which binds to endothelin A ($ET_A$) receptors on osteoblasts and stimulates their division and release of growth factors. Growth factors released during osteoblast cell division in turn stimulate the growth of metastatic prostate tumor cells. The synergy between ZD4054 and bisphosphonates was unexpected because bisphosphonates inhibit the activity of osteoclasts and are given to patients with prostate cancer not to treat the cancer, but as supportive care to relieve pain associated with bone metastases in prostate cancer. ZD4054, on the other hand, acts by inhibiting the binding of ET-1 to $ET_A$ receptors, thereby inhibiting the stimulation of osteoblastic growth and the concomitant release of growth factors which stimulate the growth of tumor cells. Since bisphosphonates act by inhibiting osteoclast activity rather stimulating the division and release of growth factors by osteoblasts, synergy was not expected.

Examiners Audet and Ha indicated that Applicant's arguments would be fully considered, but observed that the claims did not contain a limitation directed to the synergistic results. In addition, Examiners Audet and Ha suggested that Applicant review whether they can swear behind the Curwen reference with a 37 C.F.R. 1.131 declaration since it is only available as prior art under 35 U.S.C. § 102(a). Applicant undertook to review their records to determine whether they could in fact swear behind the Curwen reference.

**Inventorship Correction**

Following a review of the facts surrounding the making of the presently claimed invention in order to determine whether Applicant could swear behind the Curwen reference, it has come to Applicant's attention that Jon Owen Curwen contributed to the presently claimed invention and should be named as an inventor in addition to the presently named inventor Neil James Gallagher. Therefore, Applicant requests that Jon Owen Curwen be added as an inventor on this application.

In support of the request to correct the inventorship, we enclose the following documents:

a) A statement by Jon Owen Curwen that the error in inventorship occurred without deceptive intent on his part;

b) A combined declaration under 37 C.F.R. § 1.63 and power of attorney by Jon Owen Curwen and Neil James Gallagher;

c) A copy of an assignment by Neil James Gallagher and Jon Owen Curwen;

d) The processing fee as set forth in 37 C.F.R. § 1.17(i); and

e) Since the original inventor, Neil James Gallagher, had executed an assignment, a statement under 37 C.F.R. § 3.73(b) has also been enclosed.

**Rejection Under 35 U.S.C. § 103(a)**

The Examiner has maintained the rejection of Claims 2, 9, 11, and 27 under 35 U.S.C. §103(a) over Janus *et al*, U.S. Patent Application No. 2002/0055457 in view of Curwen *et al.*, Poster EORTC-NCI-AACR, 2002; Nelson *et al*., *BJU International* (2000), *85*(suppl. 2), p. 45-48; and Walczak *et al*., *Expert Opinion* (2002), *11*(12), p. 1737-1748. Applicant respectfully disagrees with this rejection for the reasons detailed below.

The present invention is directed to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054), or a pharmaceutically acceptable salt thereof, and a bisphosphonate.

The Examiner has stated that Janus *et al.* discloses a method of inhibition of bone metatases in cancer patients wherein the primary cancer is prostate cancer by administering an effective amount of an endothelin $ET_A$ antagonist. The Examiner further states that the method of Janus *et al.* may further comprise administration of a bisphosphonate to impede net bone loss. The

Examiner identifies the difference between Janus *et al.* and the instant invention as being the lack of disclosure in Janus *et al.* of applicant's specific $ET_A$ antagonist, ZD4054. The Examiner relies upon Curwen *et al.* for the teaching that ZD4054 is a specific endothelin A receptor antagonist which has utility in prostate cancer and metastatic bone disease. In addition, the Examiner states that Nelson *et al.* teaches that prostate cancer cell lines tested produce ET-1 mRNA and protein. Finally, the Examiner states that Walczak *et al.* teaches that men with prostate cancer are at risk for skeletal morbidity and that bisphosphonates exert their action by inducing apoptosis of osteoclasts, and have been demonstrated *in vitro* to have an inhibitory effect on breast cancer and prostate cancer cell adhesion.

Applicant respectfully submits that Curwen *et al.* is not prior art under 35 U.S.C. § 102(a), since the claimed invention was invented by Applicant prior to the effective date of the reference. Submitted with this response is a declaration under 37 C.F.R. § 1.131 executed by Jon Owen Curwen, who is an inventor of the claimed subject matter. The declaration demonstrates that the present invention was conceived before the publication of Curwen *et al.* in November 2002 and establishes diligence from a date prior to the publication of Curwen *et al.* to the date of constructive reduction to practice by filing of the above referenced patent application. Thus, Curwen *et al.* is not prior art.

None of the other references cited by the Examiner in the official action discloses the compound ZD4054 or that this particular compound would have any effect upon bone metastases. There is certainly nothing that would suggest to a person of ordinary skill in the art to combine the compound ZD4054 with a bisphosphonate in accordance with the presently claimed invention. Therefore, it is respectfully submitted that the present claims are not obvious, and we ask the Examiner to reconsider and withdraw the rejection.

**Information Disclosure Statement**

For completeness of the record we would like to bring the Examiner's attention a phase II clinical trial carried out on the compound ZD4054. This was a double-blind Phase II trial carried out in the United States on pain-free or mildly symptomatic hormone resistant prostate cancer (HRPC) patients with bone metastases. The trial was first announced on ClinicalTrials.gov (Ref. No. NCT00090363) on August 25, 2004 and the first patient enrolled was on July 14, 2004. Since the effective filing date in the United States of the instant application is September 2, 2004, this trial does not constitute a "public use" or any other prior art event under 35 U.S.C. § 102.

The primary end point of the trial was progression-free survival (PFS), and overall survival (OS) was a secondary endpoint. The trial found that although there was no significant difference in PFS, ZD4054 significantly prolonged OS compared with placebo. A summary of the trial results was published by James *et al.*, *European Journal of Cancer Supplements* (2007), Vol. 5, No. 6, abstract 3LB, see supplementary IDS).

Some of the patients in this trial also received bisphosphonates to treat the effects of bone pain associated with their cancer. An analysis of the phase II results was carried out to investigate whether there was any difference in PFS or OS between patients that received both ZD4054 and bisphosphonates and those that received ZD4054 alone. A summary of the results of this analysis are shown in Exhibit A.

The analysis found that there was no statistically significant difference in PFS or OS between the two patient groups. However, this trial was carried out on patients with metastatic cancer. As such, the trial was not able to demonstrate whether a combination of ZD4054 and a bisphosphonate would have an effect upon the formation of bone metastases, because the cancer was already metastatic when the trial commenced.

**Conclusion**

Applicant believes that the application is in condition for allowance, which action is respectfully requested.

A petition for a 3 month extension of time is being filed herewith, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 101213-1P US.

Although Applicant believes no excess claim fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No.101213-1P US.

Respectfully submitted,

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